REMARKS

Claims 1-24 are pending in the application. Claims 25 and 26 have been cancelled without prejudice as directed to non-elected subject matter. Claim 13 has been amended to correct a typographical error. These amendments add no new matter.

Allowable Claims

At page 7 of the Office Action, the Examiner stated that claims 14 and 16 are dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. For the reasons presented herein, applicants respectfully submit that all of the currently pending claims are in condition for allowance and, therefore, no amendments to dependent claims 14 and 16 are required.

35 U.S.C. §103(a)

At pages 2-5 of the Office Action, the Examiner rejected claims 1-10, 15, and 17-19, and 24 as allegedly unpatentable over Smith et al. (1998) *J. Exp. Med.* 188:17-27 ("Smith") in view of Huston et al., U.S. Patent No. 5,013,653 ("Huston") and Tudyka et al. (1997) *Protein Science*, 6:2180-87 ("Tudyka"). According to the Examiner,

> it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to make a DNA molecule encoding a fusion protein comprising a signal peptide, a fusion partner, the GST of Tudyka et al., a target protein, the soluble form of SSAO of Smith et al., and a protease cleavage site between the fusion partner and to the target protein, as outlined by Huston et al. The motivation of making such a fusion construct is to facilitate the protection, isolation and purification of the target protein. The motivation of truncating the transmembrane domain of SSAO is to produce soluble SSAO, thereby increasing the efficiency of the purification process. The motivation of using the GST of Tudyka et al. is to enable dimerization of SSAO and confers enzymatic reporter activity. The motivation of using the mutant GST of Tudyka et al. is to prevents formation of wrong crosslink formations. One of ordinary skill in the art would have had a reasonable expectation of success since the individual proteins incorporated into the fusion proteins are well known and used in the art and fusion proteins comprising a signal peptide, a target protein, any additional fused material and a cleavage site in between the target protein and the fusion partner

outlined by Huston et al. are well known and used widely in the art.

Applicants respectfully traverse the rejection in view of the following comments.

To establish a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the cited references or in the knowledge generally available to one of ordinary skill in the art, to modify a reference or to combine reference teachings to arrive at the claimed invention. In addition, there must be a reasonable expectation of success. The suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicants' disclosure. MPEP § 2143.

To arrive at the claimed invention, the skilled person would have had to have combined several separate methods which could not be combined without an inventive effort. Furthermore, nothing in the cited references provided the skilled artisan, as of the filing of the present application, with the requisite reasonable expectation that the claimed nucleic acid could have been successfully produced.

Even if a transmembrane region of a given protein has been predicted, it does not necessarily follow that a soluble form of the protein can be obtained with a reasonable expectation of success and without extensive experimentation. Before applicants' filing of the present application, it was not known which part of SSAO, if any, and/or which expression system, if any, could be used to produce a soluble and active human SSAO. Furthermore, it was not known, which fusion partner to use, where to fuse it, which signal peptide could be used for secretion of SSAO, which linker could be used between the signal peptide and GST, or which linker could be used between GST and SSAO to be able to obtain an active protein in the growth medium. The claimed invention permits the production, in milligram quantities, of pure, soluble and active human SSAO. The cited references constitute at best an invitation to vary parameters or try each of numerous possible choices until one possibly arrives at a successful result.

In Huston, a method for secretion of proteins is described. However, all proteins are unique and one cannot predict whether or where a protein can be truncated to obtain an active soluble protein. Some proteins may be inactive without a transmembrane region. According to the presently claimed invention, a region of SSAO encompassing the transmembrane region has

been replaced with a homodimeric fusion partner that facilitates the dimerization of human SSAO monomers, thereby permitting the production of active SSAO.

In Smith, the SSAO transmembrane region is predicted, but not experimentally determined. The present inventors fused the 3C protease substrate linker to amino acid no. 29 (glycine), not amino acid no. 28, which may have been a more likely choice since the transmembrane region was predicted by Smith to be amino acids 5 to 27. However, position no. 29 was carefully chosen. First, to lower the risk that the fusion protein could be cleaved by proteases in the production cell-line or in the growth medium amino acid no. 28 (arginine) was not included in the construct, because many protease substrates contain arginines. Second, glycine is the P1' amino acid in the 3C protease substrate. Third, the amino acids following G29 contain several glycines, which are small with no bulky side-chains. This means that the invention lowered the risk that the 3C protease substrate would not be accessible for cleavage by the 3C protease. For the same reason amino acids SQSQ was fused upstream of the 3C protease substrate. Q-linkers are known to be flexible and many proteins contain natural Q-linkers between domains. A flexible spacer peptide could potentially increase the accessibility of the 3C protease substrate. Thus, the combination of amino acids in the protease substrate linker and the position of the linker in the fusion protein were deliberately designed to increase the likelihood that the GST-SSAO fusion protein would be found as an intact and active protein in the growth medium, as well as be specifically and effectively cleaved between GST and SSAO after purification.

In light of these comments, applicants respectfully submit that the claimed invention is nonobvious in light of the cited references. Applicants request that the Examiner withdraw the rejection.

At pages 5-6 of the Office Action, the Examiner rejected dependent claim 11 as allegedly unpatentable over Smith in view of Huston, Tudyka, and Zambidis et al., *Proc. Natl. Acad. Sci. USA*, 93:5019-24 (1996) ("Zambidis"). Zambidis was cited in the present rejection as describing a mouse IgG1 heavy chain signal peptide.

As detailed above, Smith, Huston, and Tudyka do not provide the skilled artisan with the requisite suggestion or motivation to combine and/or modify the reference teachings to arrive, with a reasonable expectation of success, at the claimed invention. Zambidis does not add what is lacking in these references. In particular Zambidis does not indicate to the skilled artisan how to make, with a reasonable expectation of success, the nucleic acid of independent claim 1 and the claims that depend therefrom. Accordingly, applicants request that the Examiner withdraw the rejection.

At pages 6-7 of the Office Action, the Examiner rejected dependent claims 12, 13, and 20-23 as allegedly unpatentable over Smith in view of Huston, Tudyka, and Brenda Enzyme Database, EC 3.4.22.28 ("Brenda"). Brenda was cited in the present rejection as describing 3C protease amino acid sequences.

As detailed above, Smith, Huston, and Tudyka do not provide the skilled artisan with the requisite suggestion or motivation to combine and/or modify the reference teachings to arrive, with a reasonable expectation of success, at the claimed invention. Brenda does not add what is lacking in these references. In particular Brenda does not indicate to the skilled artisan how to make, with a reasonable expectation of success, the nucleic acid of independent claim 1 and the claims that depend therefrom. Accordingly, applicants request that the Examiner withdraw the rejection.

Conclusions

Applicants ask that all claims be allowed in view of the amendments and remarks contained herein.

Enclosed is a Petition for Three Month Extension of Time. Please charge the required extension fee and any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 13425-053001.

Respectfully submitted,

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